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Serial angiographic evidence of rapid resolution of coronary artery stenosis.

Sanborn TA, Faxon DP, Kellett MA, Ryan TJ.

An example of rapid, spontaneous resolution of an eccentric coronary luminal narrowing from 95 percent to 80 percent and subsequently to 50 percent stenosis over a six-week time period is presented. Spontaneous thrombolysis is proposed as the explanation for these changes and is discussed with reference to existing experimental and clinical observations.

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Carotid endarterectomy for patients with asymptomatic internal carotid artery stenosis

National Institute of Neurological Disorders and Stroke

National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

Keywords: Carotid stenosis; Endarterectomy; Stroke; Randomized trial; Carotid ultrasonography

1. Summary

On September 28, 1994, the investigators of the Asymptomatic Carotid Atherosclerosis Study (ACAS) reported the interim results of a randomized controlled clinical trial of carotid endarterectomy in patients who have asymptomatic carotid stenosis of greater than 60% reduction in diameter. In addition to aspirin and aggressive management of modifiable risk factors, one-half of the patients were randomly assigned to receive surgery after angiographic confirmation of the lesion. Carotid endarterectomy is beneficial with a statistically significant absolute reduction of 5.8% in the risk of the primary end point of stroke within 5 years and a relative risk reduction of 55%. As a consequence of the trial reaching statistical significance in favor of endarterectomy, and on the recommendation of the study's data monitoring committee, physicians participating in the study were immediately notified and advised to reevaluate patients who did not receive surgery. It is important to note that the success of the operation is dependent on medical centers and surgeons who have a documented perioperative morbidity and mortality of less than 3%, careful selection of patients, and postoperative management of modifiable risk factors.

2. Objective

The primary question of efficacy addressed by the ACAS trial was: Among patients with severe but asymptomatic carotid artery stenosis, does carotid endarterectomy, despite a perioperative risk of any stroke or death from any cause, reduce the overall 5-year risk of fatal and non-fatal ipsilateral carotid stroke (The Asymptomatic Carotid Atherosclerosis Study Group, 1989)?

3. Study sites

The trial was conducted in 39 US and Canadian centers that had been rigorously evaluated for neurological expertise, quality of the ultrasound laboratory assessment, and the quality of surgical management (Howard et al., 1991; Moore et al., 1991). The participating surgeons had met stringent criteria demonstrating a perioperative complication rate less than 3% when the indication for operation was asymptomatic carotid stenosis.

4. Patient eligibility

Patients were eligible for randomization if they were 40–79 years of age, had a life expectancy of at least 5 years, gave informed consent and had at least 60% carotid stenosis near the bifurcation of the common or internal carotid artery measured in one of the following three ways:

(A) Conventional or arterial digital subtraction angiography indicating diameter stenosis of at least 60% using minimal residual lumen (MRL) and the distal lumen (DL) in the equation $[1-(MRL/DL)]\times 100$.

(B) Doppler ultrasonography showing a peak systolic frequency or end diastolic frequency greater than the machine-specific cutpoint with predicted false positive rate of 5% determined bycorrelation of Doppler flow velocities with arteriography in 50 consecutive cases.

(C) Doppler ultrasonography showing a peak systo-

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lic frequency or end diastolic frequency greater than the machine-specific cutpoint with predicted 10% false positive *and* OPG-Gee examination pressure reduction of >5 mm Hg.

Patients were excluded for conditions which were likely to cause mortality or render follow-up difficult within the 5-year period. No patients with symptoms associated with TIA/stroke or previous endarterectomy on the randomized artery were included. Other exclusions were unstable angina pectoris, uncontrolled atrial fibrillation, severe diabetes, uncontrolled hypertension, renal insufficiency, hepatic disease, cancer, and other conditions which would confound evaluation for end points or contraindicate surgical management.

5. Intervention

After obtaining informed consent, one-half of the patients were randomly allocated to surgical management. Patients randomized to surgical management who did not have a prerandomization arteriogram, had an arteriogram prior to surgery to verify the degree of stenosis and to ascertain whether there were contraindications to endarterectomy, such as distal arterial disease. All patients were started on 325 mg of aspirin daily and aggressive reduction of modifiable risk factors.

6. Main outcome measures

The primary end point for evaluation was any stroke or death following randomization and within the 30 day perioperative period for patients receiving surgery, a comparable 42 day period from randomization for those not assigned to surgery, and any ipsilateral stroke or stroke death thereafter. All neurological symptoms and/or signs were evaluated by a neurologist. Patients were interviewed about neurologic symptoms and medical status every 3 months, alternating between telephone and in-clinic interviews. During the clinic visit, a neurologist examined the patient and the ACAS surgeon or his designee made a second assessment if symptoms or signs were found. All potential end points were adjudicated by a blinded end point review committee.

7. Main results

Between December 1987 and December 1993, 1662 eligible patients were randomized, 828 to receive surgery and 834 to medical management only. Analysis of randomized patients shows a male to female preponderance of 2:1: approximately half were between the ages of 60 and 69 and 37% were 70 or older. Ninety-five percent were Caucasian. Recognized risk factors for stroke, such as hypertension (64%), diabetes (23%), prior myocardial infarction (21%), prior contralateral TIA/stroke (25%), and smoking (26%), were balanced between the two groups.

As of July 31, 1994, the median follow-up was 2.7 years and there were 4,465 patient years of observation for endpoints. The aggregate risk of any stroke or death in the perioperative period for the surgery group was 2.3%. Of 424 post-randomization arteriograms, 31 were Doppler false positive (7.4%) and five strokes were precipitated by arteriography (1.2%). Utilizing Kaplan-Meier projections in an intention-to-treat analysis, the aggregate risk over 5 years for the primary outcome was 4.8% for patients who were assigned to receive surgery and 10.6% for patients who were treated medically. The relative risk reduction conferred by surgery was 55% (23–73%, 95% confidence interval, p=0.004).

Following endarterectomy, men had 69% relative risk reduction of primary endpoint, while women had a 16% relative risk reduction. Additional analyses and study will be required to explore the reasons for this apparent difference. The ACAS trial group is now completing follow-up, expanding the database, performing additional statistical analyses, and seeking expeditious publication of results.

8. Conclusion

Carotid endarterectomy, performed in medical centers with documented combined perioperative morbidity and mortality for asymptomatic endarterectomy of less than 3%, and on carefully selected patients who continue to have aggressive modifiable risk factor management is beneficial for patients who meet eligibility criteria of asymptomatic carotid stenosis exceeding 60% diameter reduction confirmed by arteriography.

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CAD + Fish oil

Eicosapentaenoic Acid: Its Relevance in Atherosclerosis and Coronary Artery Disease

JAWAHAR MEHTA, MD, LARRY M. LOPEZ, PharmD, and THOMAS WARGOVICH, MD

Epidemiologic studies have shown a much lower prevalence of atherosclerosis and coronary artery disease (CAD) in Greenland Eskimos and Arctic populations than in populations of Western Europe.[1,2] It has been suggested that the composition of food consumed by different populations may account for these differences in prevalence of atherosclerosis.[3] The major food consumed by the Arctic population is fish and its components such as meat, blubber and intestines. Red meat and dairy products account for only a small portion of the total diet of these people. In contrast, major dietary constituents in Western populations are red meat and dairy products.

Generally, the Arctic populations consume more protein, equivalent amounts of fat and less carbohydrate than the Western populations, but the composition of fatty acid in the diet is different. The most significant differences in the fatty acid content of diets of Eskimos and Danes are: higher content of highly polyunsaturated acids and eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids in the Arctic diet and higher linolenic acid content in the Danish diet. It has been hypothesized that a higher content of EPA derived from fish may relate to the lower prevalence of atherosclerosis and CAD in Arctic populations.[1-3]

EPA and DHA belong to the omega-3 family, which means that 1 double bond is only 3 carbon atoms away from the methyl end of the 20-carbon chain. In contrast, linolenic acid belongs to the omega-6 family of polyunsaturated fatty acids. Terrestrial plants contain not only linolenic acid, but also omega-3 α-linolenic acid, which is only sparingly converted to EPA and DHA. Fish and fish products provide large amounts of EPA and also DHA. Animal meats provide large amounts of arachidonic acid (omega-6), which is also formed by conversion of linolenic acid (Fig. 1). With consumption of diets rich in fish, fish oil or other fish-derived products, EPA content increases rapidly while arachidonic acid content decreases in platelet, leukocyte and other tissue membrane phospholipids.

In this article we review the relevance of EPA in atherogenesis and CAD. We discuss the pathogenesis of atherosclerosis, role of platelets and leukocytes in CAD and potentially beneficial effects of EPA in atherogenesis and CAD.

Atherogenesis: It has been suggested that critical interactions between 4 types of cells—monocytes, platelets, endothelial cells and smooth muscle cells—are involved in atherogenesis.[4] In cholesterol-fed monkeys, the initial lesion is deposition of cluster of leukocytes, principally monocytes, on arterial endothelium. These monocytes migrate subendothelially and take on the shape of foam cells in fatty streaks. The overlying endothelium retracts and provides opportunity for platelet adherence, aggregation and mural thrombosis. Smooth muscle proliferation and migration from media to the intima and accumulation of lipids within the smooth muscle cells are prominent features of fibrous plaque formation.

Platelet activation is particularly important in atherogenesis in hypercholesterolemia,[4] homocystinuria,[5] after injury induced by intraarterial catheters,[6] or at perianastomotic sites after bypass surgery.[7] Loss of endothelial continuity permits platelet adhesion and release of platelet products such as thromboxane A_2 and platelet-derived growth factor. This growth factor is produced by activated platelets as well as by monocytes, endothelial cells and smooth muscle cells and is a potent chemotactic and mitogenic factor.

Secretion of thromboxane A_2, platelet factor 4, β-thromboglobulin and products of lipoxygenase path-

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way from activated platelets may contribute to initial intramural thrombus formation and development of atherosclerosis.[8] Binding of platelet-derived growth factor to its receptor results in phospholipase activation and increased release of free arachidonic acid[9] as well as new cyclooxygenase synthesis.[10] Monocytes/macrophages produce potent chemoattractant leukotriene B_4, a product of arachidonic acid through the lipoxygenase pathway. Clusters of leukocytes also produce other leukotrienes (such as C_4, D_4 and E_4), which promote platelet aggregation[11] and cause vascular constriction[12] and may be important in reduced blood flow during and after atherogenesis.

Elevated levels of plasma lipoproteins, especially low and very low density fractions, are often associated with increased incidence of atherosclerosis. Hyperlipidemia may participate in atherogenesis by injury to endothelium by increased membrane viscosity.[13] This could help to explain endothelial retraction in atherosclerotic plaques. Hyperlipidemic endothelium may also permit monocyte adhesion, an early step in atherogenesis, and may induce growth factor formation in endothelial cells. Other effects of hyperlipidemia may involve alterations in smooth muscle cells, platelets and monocytes. Thus, atherosclerosis is a complex process that involves important perturbations in "cell-cell interaction," lipoprotein metabolism, arachidonic acid metabolism and perhaps several other factors.

Platelets, leukocytes, prostaglandins and leukotrienes in coronary artery disease: A variety of platelet abnormalities consistent with platelet hyperactivity have been identified in patients with CAD, especially those with acute myocardial ischemia.[14] Coagulation cascade is also activated after platelet adhesion to exposed subendothelial collagen and microfibrils at the sites of atherosclerotic plaque rupture, arteriovenous anastomosis or angioplasty. There is evidence for increased neutrophil aggregation in vitro in patients with acute myocardial infarction[15] and accumulation of mast cells in the coronary arteries of patients with vasospastic angina,[16] which may contribute to myocardial ischemia by release of leukotrienes, histamine and prostaglandins. These abnormalities in platelet and leukocyte function could be responsible for thrombus formation in narrowed coronary arteries as well as propagation of atherosclerotic process.

Infiltration of leukocytes in a "platelet clot" or in infarcted myocardium was previously believed to involve a passive inflammatory process. Leukocyte accumulation is now considered an active process[17-20] that determines the size of the arterial thrombus or myocardial infarct. Leukocytes promote endothelial injury through release of free oxygen radicals. Leukocyte-released products cause platelet activation, vasoconstriction, increased vascular permeability and neutrophil migration. Inhibition of leukocyte function (by pharmacologic agents) or number (by use of antineutrophil serum) does indeed decrease platelet deposition in the ischemic myocardium and reduce the size of intracoronary thrombus and infarct in animal models of myocardial ischemia.[17-20]

Arachidonic acid, derived from dietary sources (mostly animal meats) as well as from conversion of linolenic acid (Fig. 1) is a major component of membrane phospholipids. It is a 20-carbon structure with 4 double bonds (C20:4). It is converted in platelets through the cyclooxygenase pathway to products with 2 double bonds, such as thromboxane A_2, a potent vasoconstrictor and platelet aggregant, and in blood vessels to prostaglandin I_2 or prostacyclin, a potent vasodilator and platelet inhibitor.[14] Excessive thromboxane A_2 release has been incriminated in the genesis and propagation of atherosclerosis[8] and myocardial ischemia resulting in unstable angina pectoris and acute myocardial infarction.[14] In leukocytes, arachidonic acid is converted through the lipoxygenase pathway to leukotrienes of the 4-series and hydroxy-fatty acids (Fig. 2). Leukotriene B_4 causes increase in vascular permeability and leukocyte chemotaxis, and leukotrienes C_4 and D_4 cause coronary artery constriction[12] and platelet activation.[11]

Eicosapentaenoic acid: EPA is a 20-carbon structure with 5 double bonds. It is readily incorporated into the cell membrane phospholipid. However, it is a poor substrate for cyclooxygenase enzyme, and its me-

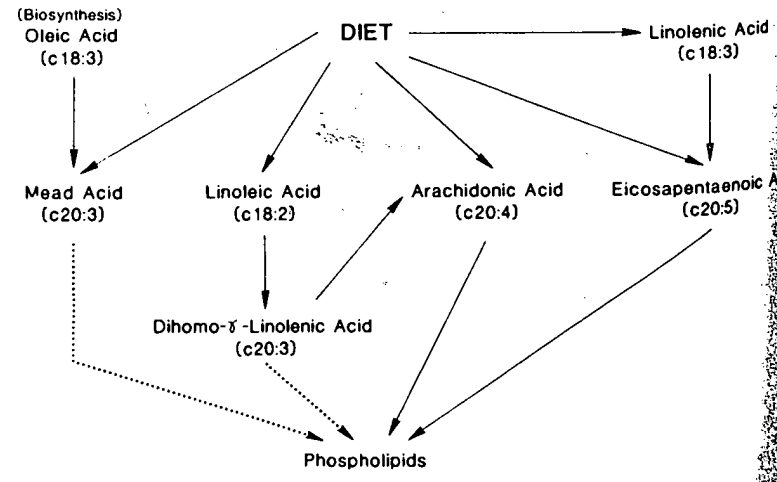

FIGURE 1. Linolenic acid (C18:2, W-6) is obtained primarily from terrestrial plants, and arachidonic acid (C20:4, W-6) from animal meat or via desaturation and chain lengthening of linolenic acid. Eicosapentaenoic acid (C20:5, W-3) is obtained from fish or via conversion of linolenic acid (C18:3, W-3). Oleic acid can be synthesized de novo or obtained from the diet.

tabolism results in formation of small amounts of end products with 3-double bonds, such as thromboxane A_3 and prostaglandin I_3 (Fig. 3). Simultaneously, thromboxane A_2 and prostaglandin I_2 production decreases. Thromboxane A_3 is considerably less potent than its counterpart thromboxane A_2, but prostaglandin I_3 has biologic activity similar to prostaglandin I_2. EPA, however, is a preferential substrate for lipoxygenase enzyme with subsequent formation of leukotrienes of the 5-series, which are much less potent than leukotrienes of 4-series. These alterations in Arctic populations are associated with increased bleeding times, reduction in platelet aggregation in response to arachidonic acid and collagen, and a low incidence of atherosclerosis and CAD.[1,2]

When placed on a supplemental fish diet, cod liver oil or EPA, Western Europeans show changes in platelet function similar to those of the Arctic populations.[21-26] Even 10 ml/day of 50% EPA or 500 to 800 g/day of mackerel for 2 to 3 weeks is enough to cause these potentially beneficial effects. EPA content in platelet membrane increases with a resultant decline in platelet aggregation and thromboxane A_2 generation and an associated increase in bleeding time. EPA also causes additional prolongation of bleeding time after aspirin. EPA decreases blood viscosity, an effect related probably to alterations in lipid content of red blood cell membranes.[25,26]

Another potentially beneficial effect of EPA is a change in serum lipid levels. The onset of this action is rapid and the near-maximal lipid-lowering effect usually occurs within 2 to 4 weeks,[27-29] although further decreases may occur up to 2 years after starting therapy.[27] The major effect of EPA on lipoproteins is reduction in circulating triglyceride levels. Changes in total cholesterol and low-density lipoprotein levels are less pronounced and unpredictable. High-density lipoprotein levels are usually unchanged or may slightly increase. The lipid-lowering effect of EPA is directly proportional to pretreatment triglyceride levels.[28] The mechanism of the lipid-lowering effect of EPA is not known, but omega-3 and omega-6 fatty acids stimulate fecal output of neutral or acidic sterols or both.[30] Fish oils also decrease serum lipoprotein levels by inhibiting hepatic lipogenesis,[31] thereby decreasing lipoprotein synthesis and secretion.

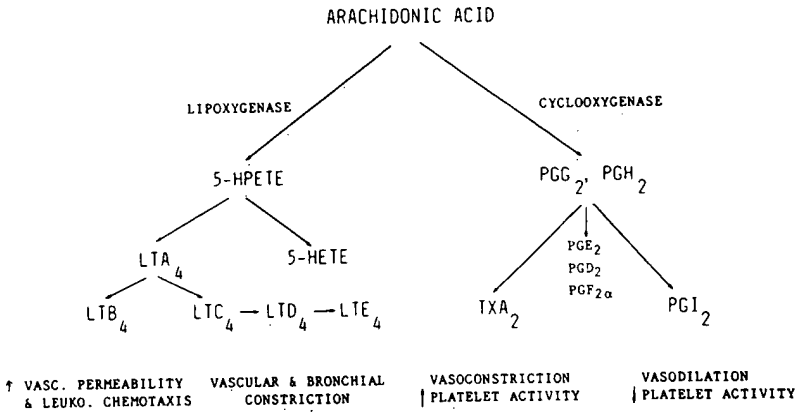

FIGURE 2. Arachidonic acid metabolism results in formation of thromboxane A_2 (TXA_2) in platelets, prostacyclin (PGI_2) in the blood vessels, and leukotrienes (LTs) of 4-series and hydroxy eicosatetraenoic acid (HETE) primarily in the leukocytes. The biologic effects of TXA_2, PGI_2 and LTs are mentioned. Prostaglandins E_2, D_2, and $F_{2\alpha}$ are less potent than TXA_2 or PGI_2 in their biologic activity.

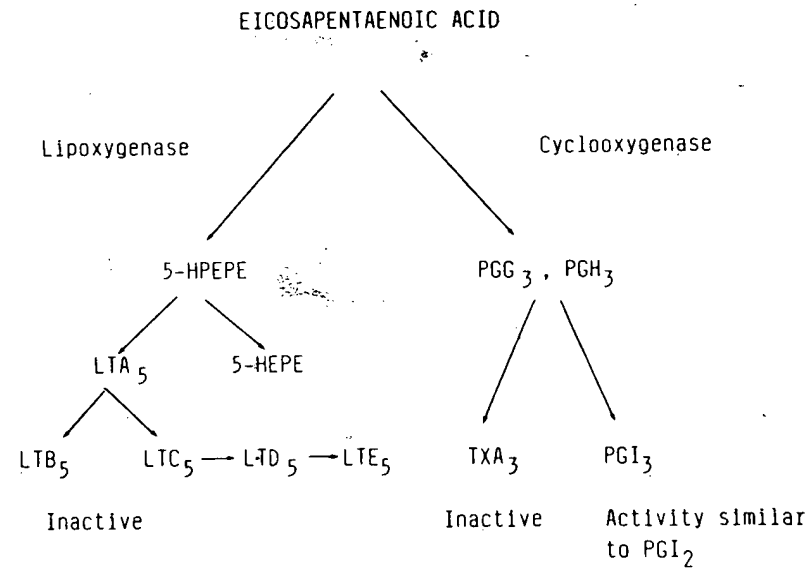

FIGURE 3. Eicosapentaenoic acid metabolism results in formation of inactive thromboxane A_3 (TXA_3) and leukotrienes (LTs) of the 5-series. PGI_3 has biologic activity similar to that of PGI_2.

These effects, particularly reduction in platelet activity and lipoproteins, and production of thromboxane A_3, prostaglandin I_3 and leukotrienes of 5-series could favorably influence formation of intravascular thrombus in atherosclerotic coronary arteries and progression of atherosclerosis.

Trials of fish, fish oil and eicosapentaenoic acid: Fish oil is a heterogenous mixture of fatty acids. Omega-3 EPA and DHA are especially prevalent in fish flesh, with a range of 0.1 to 90% by weight among different species. Among fish in the Western diet, Pacific oysters, herring, anchovy, salmon, albacore tuna, Pacific halibut and mackerel are rich in omega-3 fatty acids. Most studies have used a commercial fish oil preparation called Max-EPA or cod liver oil. According to the manufacturer, Max-EPA consists of a refined blend of marine body oils in which the total fatty acid content contains at least 18% EPA and at least 12% DHA, with a trace amount of cholesterol (0.6% w/w). Max-EPA is marketed in bulk liquid either as mint-flavored and emulsified or as unflavored and nonemulsified; the latter has a strong, cod liver-like odor. One tablespoon (15 ml) of the emulsified oil provides 1 g of EPA and 670 mg of DHA. Max-EPA is also available as gelatin capsules containing 180 mg EPA and 120 mg DHA. The bulk and encapsulated preparations are sold in this country only through "health food" stores and nutrition-oriented magazines. Cod liver oil contains 6 to 11% EPA and 6 to 16% DHA.

Administration of EPA to animals results in reduction in size of experimental cerebral and myocardial infarction.[32,33] In a study in swine with cholesterol-induced atherosclerosis, dietary supplementation with cod liver oil caused a significant decrease in the degree of coronary atherosclerosis (Table I).[34]

TABLE I Cod Liver Oil and Coronary Atherosclerosis (Luminal Encroachment, %) in Swine

	Right Coronary	LAD	LCx Segments with Atheroma
Control	54	44	43
Cod liver oil	13	11	5
p value	0.02	0.02	0.02

Adapted from Weiner et al.[34]
LAD = left anterior descending coronary artery; LCx = left circumflex artery.

In 13 patients with CAD, administration of 20 ml/day of Max-EPA for 5 weeks resulted in an increase in platelet survival and a decrease in platelet and leukocyte counts. Plasma levels of β-thromboglobulin and platelet factor 4 also decreased, indicating reduction in platelet release reaction.[24] However, no data were provided on the status of angina pectoris. In another study,[27] 107 patients with angina pectoris were given EPA (1.8 to 3.6 g/day) and observed for 2 years. Serum triglyceride levels decreased rapidly; cholesterol levels also decreased, but slowly. High-density lipoprotein levels increased and very low density lipoprotein levels decreased. Bleeding time increased. Most important, nitroglycerin consumption declined from almost 30 to only 5 tablets/week, but there were no objective data to quantitate reduction in myocardial ischemia. In a recent study,[29] 6 patients with peripheral vascular disease were given EPA, 10 g/day for 1 month. Thromboxane A_2 formation declined by 58% and platelet function was moderately suppressed. No data were provided relative to any change in symptoms of peripheral vascular disease.

We studied 8 patients with CAD and angina pectoris whose diet was supplemented with 3.2 g/day of EPA or placebo in a randomized, double-blind fashion over a 12-week period. With EPA supplementation, platelet and neutrophil count decreased slightly. Platelet aggregation in response to epinephrine and collagen decreased variably, but neutrophil aggregation decreased consistently. Leukotriene B_4 and thromboxane A_2 formation declined by 25% and 45%, respectively. Concomitant with these changes, triglyceride levels fell 47% and high-density lipoprotein levels increased 15%. Blood pressure, heart rate and double product were lower at rest as well as during exercise, indicating reduction in myocardial oxygen demand. However, angina frequency and nitroglycerin consumption and exercise performance were unchanged.

These data could be interpreted to imply that thromboxane A_2, leukotrienes and platelet activation are not involved in myocardial ischemia or alternatively, it is possible that long-term therapy with EPA is necessary to observe a significant change in the course of CAD.

Beneficial effects of long-term therapy are exemplified by a recent epidemiologic study in a Dutch population,[35] which showed an inverse correlation between consumption of fish and prevalence of cardiac death during a 20-year follow-up. This study was conducted in a prospective fashion and an average intake of only 30 g/day of fish had a substantial protective effect against cardiac death. The inverse relation between fish consumption and cardiac death appeared to be independent of other risk factors, such as age, blood pressure and serum cholesterol levels. Data for mortality from cancer or other diseases were not provided.

Future directions: Fish, fish oil and EPA may have an important role as dietary supplements in primary and in secondary prevention of atherogenesis and its complications. Questions in the cardiovascular area are: (1) Does long-term administration of EPA limit progression or cause regression of atherosclerotic lesions? (2) Does EPA therapy prevent or beneficially influence the mortality and morbidity rate among patients with unstable angina and acute myocardial infarction? (3) Does EPA have a role in prevention of closure of coronary arteries after angioplasty? (4) Does EPA have a role in prevention of coronary artery bypass graft closure? (5) Does EPA cause a sustained decrease in blood pressure either alone or in conjunction with other pharmacologic agents in hypertensive subjects? (6) Does long-term administration of EPA prevent episodes of angina pectoris and improve objective measures of exercise performance in patients with stable CAD?

Caution is necessary relative to unknown but possible side effects from EPA therapy. Reduction in platelet function and prolongation of bleeding time may be associated with bleeding diathesis. Impaired leukocyte function may lead to loss of immunity with its attendant complications, such as infection, delayed healing after tissue injury and carcinogenicity.

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STIC-ILL

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Clinical Advisory

Carotid endarterectomy for patients with asymptomatic internal carotid artery stenosis

National Institute of Neurological Disorders and Stroke

National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

Keywords: Carotid stenosis; Endarterectomy; Stroke; Randomized trial; Carotid ultrasonography

1. Summary

On September 28, 1994, the investigators of the Asymptomatic Carotid Atherosclerosis Study (ACAS) reported the interim results of a randomized controlled clinical trial of carotid endarterectomy in patients who have asymptomatic carotid stenosis of greater than 60% reduction in diameter. In addition to aspirin and aggressive management of modifiable risk factors, one-half of the patients were randomly assigned to receive surgery after angiographic confirmation of the lesion. Carotid endarterectomy is beneficial with a statistically significant absolute reduction of 5.8% in the risk of the primary end point of stroke within 5 years and a relative risk reduction of 55%. As a consequence of the trial reaching statistical significance in favor of endarterectomy, and on the recommendation of the study's data monitoring committee, physicians participating in the study were immediately notified and advised to reevaluate patients who did not receive surgery. It is important to note that the success of the operation is dependent on medical centers and surgeons who have a documented perioperative morbidity and mortality of less than 3%, careful selection of patients, and postoperative management of modifiable risk factors.

2. Objective

The primary question of efficacy addressed by the ACAS trial was: Among patients with severe but asymptomatic carotid artery stenosis, does carotid endarterectomy, despite a perioperative risk of any stroke or death from any cause, reduce the overall 5-year risk of fatal and non-fatal ipsilateral carotid stroke (The Asymptomatic Carotid Atherosclerosis Study Group, 1989)?

3. Study sites

The trial was conducted in 39 US and Canadian centers that had been rigorously evaluated for neurological expertise, quality of the ultrasound laboratory assessment, and the quality of surgical management (Howard et al., 1991; Moore et al., 1991). The participating surgeons had met stringent criteria demonstrating a perioperative complication rate less than 3% when the indication for operation was asymptomatic carotid stenosis.

4. Patient eligibility

Patients were eligible for randomization if they were 40–79 years of age, had a life expectancy of at least 5 years, gave informed consent and had at least 60% carotid stenosis near the bifurcation of the common or internal carotid artery measured in one of the following three ways:

(A) Conventional or arterial digital subtraction angiography indicating diameter stenosis of at least 60% using minimal residual lumen (MRL) and the distal lumen (DL) in the equation $[1-(MRL/DL)]\times 100$.

(B) Doppler ultrasonography showing a peak systolic frequency or end diastolic frequency greater than the machine-specific cutpoint with predicted false positive rate of 5% determined bycorrelation of Doppler flow velocities with arteriography in 50 consecutive cases.

(C) Doppler ultrasonography showing a peak systo-

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lic frequency or end diastolic frequency greater than the machine-specific cutpoint with predicted 10% false positive *and* OPG-Gee examination pressure reduction of >5 mm Hg.

Patients were excluded for conditions which were likely to cause mortality or render follow-up difficult within the 5-year period. No patients with symptoms associated with TIA/stroke or previous endarterectomy on the randomized artery were included. Other exclusions were unstable angina pectoris, uncontrolled atrial fibrillation, severe diabetes, uncontrolled hypertension, renal insufficiency, hepatic disease, cancer, and other conditions which would confound evaluation for end points or contraindicate surgical management.

5. Intervention

After obtaining informed consent, one-half of the patients were randomly allocated to surgical management. Patients randomized to surgical management who did not have a prerandomization arteriogram, had an arteriogram prior to surgery to verify the degree of stenosis and to ascertain whether there were contraindications to endarterectomy, such as distal arterial disease. All patients were started on 325 mg of aspirin daily and aggressive reduction of modifiable risk factors.

6. Main outcome measures

The primary end point for evaluation was any stroke or death following randomization and within the 30 day perioperative period for patients receiving surgery, a comparable 42 day period from randomization for those not assigned to surgery, and any ipsilateral stroke or stroke death thereafter. All neurological symptoms and/or signs were evaluated by a neurologist. Patients were interviewed about neurologic symptoms and medical status every 3 months, alternating between telephone and in-clinic interviews. During the clinic visit, a neurologist examined the patient and the ACAS surgeon or his designee made a second assessment if symptoms or signs were found. All potential end points were adjudicated by a blinded end point review committee.

7. Main results

Between December 1987 and December 1993, 1662 eligible patients were randomized, 828 to receive surgery and 834 to medical management only. Analysis of randomized patients shows a male to female preponderance of 2:1: approximately half were between the ages of 60 and 69 and 37% were 70 or older. Ninety-five percent were Caucasian. Recognized risk factors for stroke, such as hypertension (64%), diabetes (23%), prior myocardial infarction (21%), prior contralateral TIA/stroke (25%), and smoking (26%), were balanced between the two groups.

As of July 31, 1994, the median follow-up was 2.7 years and there were 4,465 patient years of observation for endpoints. The aggregate risk of any stroke or death in the perioperative period for the surgery group was 2.3%. Of 424 post-randomization arteriograms, 31 were Doppler false positive (7.4%) and five strokes were precipitated by arteriography (1.2%). Utilizing Kaplan-Meier projections in an intention-to-treat analysis, the aggregate risk over 5 years for the primary outcome was 4.8% for patients who were assigned to receive surgery and 10.6% for patients who were treated medically. The relative risk reduction conferred by surgery was 55% (23–73%, 95% confidence interval, p=0.004).

Following endarterectomy, men had 69% relative risk reduction of primary endpoint, while women had a 16% relative risk reduction. Additional analyses and study will be required to explore the reasons for this apparent difference. The ACAS trial group is now completing follow-up, expanding the database, performing additional statistical analyses, and seeking expeditious publication of results.

8. Conclusion

Carotid endarterectomy, performed in medical centers with documented combined perioperative morbidity and mortality for asymptomatic endarterectomy of less than 3%, and on carefully selected patients who continue to have aggressive modifiable risk factor management is beneficial for patients who meet eligibility criteria of asymptomatic carotid stenosis exceeding 60% diameter reduction confirmed by arteriography.

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PREVENTION OF ATHEROSCLEROTIC ARTERIAL STENOSIS AND RESTENOSIS AFTER ANGIOPLASTY WITH ANDROGRAPHIS PANICULATA NEES AND FISH OIL

EXPERIMENTAL STUDIES OF EFFECTS AND MECHANISMS

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Restenosis rate after coronary angioplasty has been up to 30%–40%. To solve this problem, we studied the effects of *Andrographis Paniculata Nees* (APN) and fish oil (FO, ω3 polyunsaturated fatty acids over 70%) on atherosclerotic stenosis and restenosis after experimental angioplasty and the relevant mechanisms of APN and FO. Preliminary results showed that APN can significantly alleviate atherosclerotic iliac artery stenosis induced by both deendothelialization and high cholesterol diet (HCD) and restenosis following angioplasty in rabbits. FO showed the same but milder effects than APN did. Both APN and FO significantly inhibited blood monocytes to secrete growth factors in vivo. Ca^{++} –ATPase activity of cell membrane of atherosclerotic rabbits was significantly decreased, while APN or FO, especially the former alleviated this reduction. Refined extract of APN significantly decreased in vitro resting platelet $[Ca^{++}]i$ and in vivo the resting and thrombin–stimulated platelet $[Ca^{++}]i$ after oral administration of APN for 2 weeks. APN significantly inhibited cell growth or DNA synthesis in dose–dependent manner. In conclusion because of the machanisms described above, APN can alleviate atherosclerotic artery stenosis induced by both deendothelialization and HCD as well as lower restenosis rate after experimental angioplasty. The effects of APN are evidently superior to those of FO.

Percutaneous transluminal coronary angioplasty (PTCA) is an established and widely used tachnique for the treatment of coronary artery disease, but restenosis incidence after PTCA is high up to 30%–40%.[1–6] This problem has not been solved despite the use of anticoagulants, antiplatelet agents, calcium channel blockers, antineoplastic therapy, and various interventional manoeuvres.[1–6] To tackle this problem, we investigated the action of the extract of *Andrographis Paniculata Nees* (APN) and fish oil (FO) on atherosclerotic stenosis and restenosis after angioplasty in rabbit model with iliac artery stenosis. The mechanisms of these drugs were explored.

MATERIAL AND METHODS

Preventive effect of APN or FO on atherosclerotic iliac stenosis. Twenty–two Japanese male white rabbits were randomly divided into 3 groups: control group, 10 rabbits; APN preventive group, 5 rabbits; and FO preventive group, 7 rabbits. All rabbits were fed with a 2% high cholesterol diet. In APN preventive group, 2 pills of APN (4.0 g crude APN / pill) were given b.i.d. for 3 days, and in FO group 2 pills of FO (0.45 g, omega–3 polyunsaturated fatty acid over 70%) b.i.d. for 3 days. Three days later, bilateral iliofemoral Gruentzig balloon endothelial denudation was performed.[7] Further cholesterol diet with or without preventive drug was fed for 7 weeks cousecutively in the 3 groups. Blood samples were drawn to observe the following parameters: activity of red blood cell membrane ATPases; response of monocytes to APN or FO in releasing growth fac-

tors (or mitogenic factors). Then aortoiliac angiography was performed to observe the degree of stenosis and the effect of the drugs on stenosis.

Preventive effect of APN and FO on restenosis after angioplasty. Twenty–six Japanese male white rabbits underwent right iliofemoral artery endothelial denudation with the method described above. High cholesterol diet was fed for 7 weeks, and abdominal angiography was performed. Twenty–four rabbits showed various degrees of stenosis of the right iliac artery. They were randomly divided into 3 groups (control 8 rabbits, APN 8, and FO 8). The 2 preventive groups received APN or FO 2 pills b.i.d. for 3 days respectively. Balloon angioplasty was performed according to the standard procedure. The balloon was inflated 3 times, and dilation of the artery was confirmed angiographically. These rabbits were fed again with high cholesterol diet with or without APN or FO respectively for 4 weeks. Angiography was done to observe whether there is the restenosis of the right iliac artery.

Angiographic assessment of stenosis and restenosis. The luminal diameter stenosis was accessed by a consensus of 2 observers (one without konwledge of treatment). Caliper measurements were taken at the samllest luminal diameter narrowing. The percentage of stenosis was calculated in comparison with the neighboring or opposite normal iliac artery. The severity of stenosis was calculated by the formula: the percentage of stenosis × length (mm) of narrowing. Thus the severity of stenosis was classified as: class I = scores < 449, class II = scores 500 – 999, class III > 1000, class IV = stenosis over 90% or of total occlusion.

Mechanisms of APN and FO in prevention of restenosis. We observed the suppressive effect of APN or FO on release of growth factors or mitogenic factors by cultured blood monocytes with reference to activation of concanavalin A.[8,9] The monocytes conditioned media (MCD) were used for culture of fibroblasts. ^{3}H–thymidine (^{3}H–TdR) was incorporated into the cultured fibroblasts for liquid scintillation counting. The suppressive effect of APN or FO on fibroblast growth was compared with that in normal or atherosclerotic model group. The changes of Ca^{++}–ATPase, Mg^{++}–ATPase and Na^+–K^+–ATPase activity of red blood cell membrane of different groups of rabbits were measured by Vincenzi's and Chen's method.[10,11] The effects of APN on rabbit platelet cytosolic free calcium concentration ($[Ca^{++}]_i$) were observed. In experiments in vitro we observed refined AP isolate, API_{0134}. Platelets of the blood drawn from rabbits ($n = 6$) were separated and loaded with fluorescence indicator Fura–2 / AM in platelet suspension. The suspension was then divided into two parts, one for control another added with API_{0134}. The platelet $[Ca^{++}]i$ was calculated by the formula[12]:

$$[Ca^{++}]i(nM) = Kd\frac{F - Fmin}{Fmax - F}$$

In experiment in vivo, resting and thrombin stimulated platelet $[CA^{++}]i$ was measured. 6 rabbits were given 3 pills of APN b.i.d. for 15 days. The values of platelets $[Ca^{++}]i$ measured were compared with those before administration of APN. Inhibitory action of API_{0134} on growth of cultured fibroblasts was observed. Seed fibroblasts were collected by the method described above.[8,9] After 24–hour culture, the media were replaced by M_{199} media containing 5% fetal bovine serum with API_{0134} 75μg / ml, 150μg / ml or 300μg / ml or without any drug (as control) respectively. ^{3}H–TdR was added, the incorporated ^{3}H–TdR was counted by the method above, and then the efficacy of API_{0134} was calculated in inhibiting growth of fibroblasts or DNA synthesis.

RESULTS

The preventive effect of APN and FO on atherosclerotic iliac stenosis. *Control group* (Table 1). Angiographically, all 20 arteries(100%) in 10 rabbits showed various degrees of stenosis (25%–100%, average 60.53% ± 31.03%), 6 of them were completely occluded. Microscopically, the media of the affected vessels were thinned, while the intima was remarkably thickened, overfilled with a large amount of foam cells. The lumina were severely stenosed or occluded (Fig 1A).

APN group. 7(70%) of 10 iliac arteries showed stenosis (12%–48%, average 26.39% ± 10.52%); mild to moderate intimal hyperplasia was demonstrated (Fig 1B).

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Table 1. Grades of stenosis in different groups of rabbits

Group	Tn	Ln	Vessel (%)	class I n(%)	Class II n(%)	Class III n(%)	Class IV n(%)
Control	20	20	(100)	5(250)	5(25)	3(15)	7(35)
FO	14	10	(71.4)*	2(20)	3(30)	4(40)*	1(10)**
APN	10	7	(70)*	6(86)**	1(14)**	0	0

Tn = total deendothelialized iliac artery number; *Ln* = lesion artery number. * $P<0.05$, * * $P<0.01$, compared with the control group.

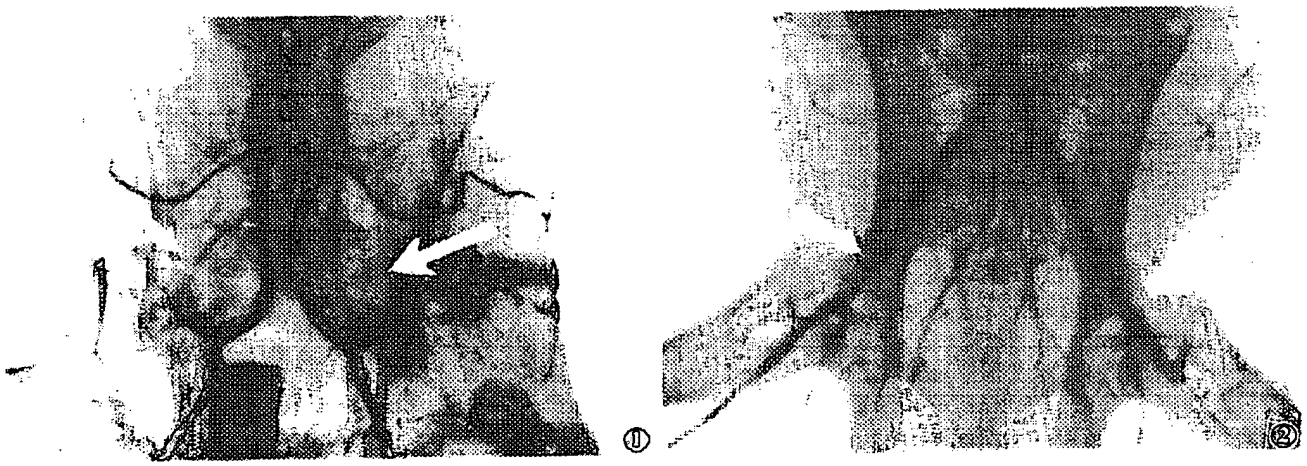

Fig 1. ① The aortic–iliac artery angiogram in rabbits of control group showing total occlusion of bilateral external iliac arteries with compensative dilation of bilateral internal iliac arteries; ② The aortic–iliac artery angiogram of preventive APN–treating rabbit showing slight stiffening of bilateral iliac arteries with mild narrowing of the right iliac artery.

FO group. 10(71%) of 14 iliac arteries showed various degrees of stenosis (14%–100%, average 53% ± 21.2%), and one artery showed total occlusion. Intima showed prominent hyperplasia but milder than that seen in the control group.

Preventive effect of APN and FO on restenosis aft r angioplasty. *Control group.* The severity of stenosis before angioplasty was 33%–100%, average 63.3% (class IV, 1 vessel; class III and class II, the remaining vessels); the residual stenosis immediately after angioplasty was 0–20%. Four weeks after angioplasty restenosis occurred in all rabbit models (5%–100%, mean value 76%) and the length of lesions protracted longer. The rabbit with total occlusion before angioplasty showed reocclusion 2 weeks after angioplasty (Fig 2A–C).

APN group. Before angioplasty, the severity of stenosis was 32%–100%, mean 60.4% (class IV, 1 vessel, class III and II the remaining vessels). The residual stenosis immediately after angioplasty was 0–15%. Four weeks after angioplasty the rate of restenosis was 0–36% (mean 17.5%, Fig 3A–C), much moderate than that occurred in the control group.

FO group. Before angioplasty, the stenosis was around 46% (class I or II), and the residual stenosis 0–19%.

Angiographic results before, immediately and 4 weeks after angioplasty are shown in Table 2.

Table 2. The results (stenosis degree) before, immediately and 4 weeks after angioplasty

Group	Before	Immediate	Four weeks later
Control	33%–100%(63.3%)	0–10%	52%–100%(76%)
FO	40%–50%(46.0%)	0–19%	30%–58%(44%)*
APN	32%–100%(60.4%)	0–15%	0%–36%(17%)**

* Compared with the control, $P<0.05$

* * Compared with the control, $P<0.01$

Changes of ATPase activities of RBC membrane and its resp nse to APN and FO. The changes of Ca^{++}–ATPase, Mg^{++}–ATPase and Na^{+}–K^{+}–ATPase and their differences are listed in Table 3.

The results show that there is no difference of Mg^{++}–ATPase in different groups. But the activity of Ca^{++}–ATPase was markedly reduced in the atherosclerotic model group than the normal group and Na^{+}–K^{+}–ATPase significantly increased. In APN and FO treated groups, the activity of Ca^{++}–ATPase resembled that of normal groups.

Inhibitory action of APN and FO on monocytes

Table 3. Activities of Ca^{++}–ATPase, Mg^{++}–ATPase and Na^{+}–K^{+}–ATPase of RBC membrane

Group	Ca^{++}–ATPase	Mg^{++}–ATPase	Na^{+}–K^{+}–ATPase
Control($n=8$)	11.64 ± 1.95	10.50 ± 1.03	1.80 ± 0.69
AS ($n-15$)	5.38 ± 2.75*	8.54 ± 1.42	5.87 ± 1.70*
APN ($n=6$)	10.44 ± 5.03**	11.31 ± 1.62	2.94 ± 3.07
FO ($n=6$)	9.12 ± 4.00**	11.85 ± 2.67	6.06 ± 3.348

* Compared with the control. $P<0.05$. * * Compared with the control. $P<0.01$.

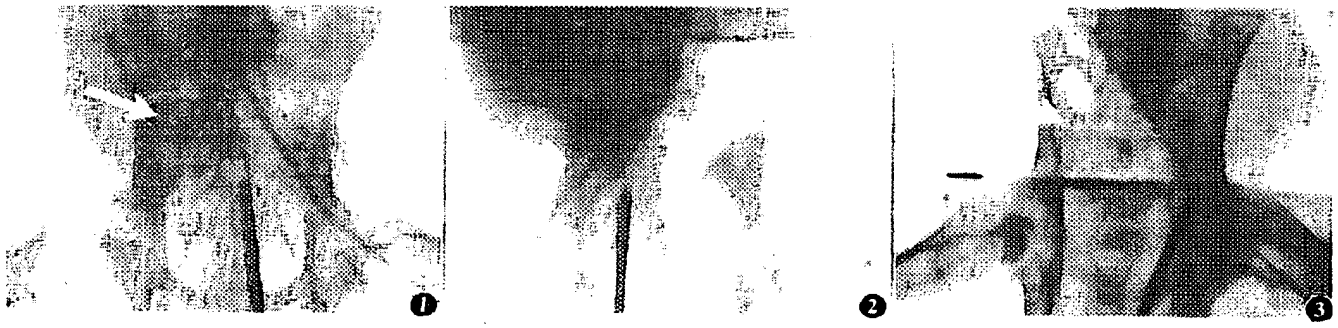

Fig 2. The right iliac artery angiograms in rabbit of control group before, immediately and 4 weeks after angioplasty. ① the total occlusion of rabbit 5 weeks before angioplasty; ② successful angioplosty without residual restenosis; ③ reocclusion 2 weeks after angioplasty.

Fig 3. The right iliac artery angiograms of APN–preventing rabbit before, immediately and 4 weeks after angioplasty. ① the right external iliac artery stenosis (40%) before angioplasty; ② successful balloon angioplasty without residual stenosis; ③ mild restenosis (25%) 4 weeks after the procedure.

to secrete growth factors (or mitogenic factors). Con–A stimulated monocytes in the normal and atherosclerotic control groups secrete a great amount of growth factors to enhance the growth of fibroblasts, but this response in the APN and FO treated group, especially APN group was

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significantly inhibited (Fig 4).

Effects of APN on platelet $[Ca^{++}]i$ in vitro. The resting platelet $[Ca^{++}]i$ in the API_{0134} treated group

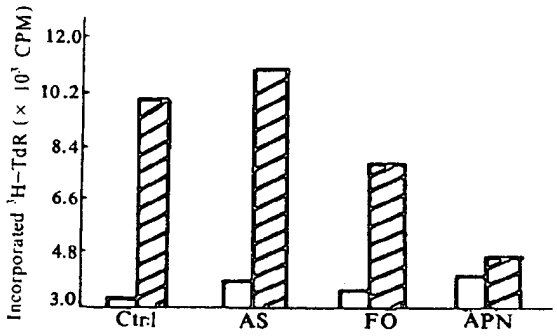

Fig 4. The incorporated ^3H-TdR(CPM) difference of various groups before and after stimulation of Con-A and effect of APN- or FO-feeding on 3H-TdR incorporation after Con A-stimulation. Ctrl, AS, FO and APN represents normal control group, atherosclerosis group FO-treated and APN treated group. □ without Con A, 2.23 (Ctrl), 3.92 (AS), 3.56 (FO), 4.30 (APN); ▨ with Con A, 9.24 (Ctrl), 11.87 (AS), 7.79 (FO), 4.69 (APN).

(155.74 = 31.19) was significantly lower than that in the normal control (207.89 ± 22.81) ($P < 0.05$), while the resting $[Ca^{++}]i$ in vivo after treatment with APN (159.32 ± 18.53) was significantly lower than pretreatment concentration. The thrombin-stimulated platelets $[Ca^{++}]i$ showed beneficial effects of APN i.e. pretreatment with APN the platelet $[Ca^{++}]i$ was 448.5+79.02 and dropped to 340.17 ± 59.89 after treatment ($P < 0.01$).

Inhibitory action of API_{0134} *on growth of fibroblasts (Fig 5).* The results showed that API_{0134} significantly inhibited the DNA synthesis or hyperplasia of serum-cultured fibroblasts in the manner of dose-dependence, inhibitory rate being 26.1%, 45.0%, 61.3%, in respect to various dosages of API_{0134} of 75 μg / ml, 150 μg / ml and 300 μg / ml.

DISCUSSION

Pathological studies have provided insights into the mechanisms of restenosis after PTCA. These mechanisms involve a series of events leading to restenosis i.e. endothelial injury and denudation, tear of intima or even media may lead to platelet deposition and aggregation, formation of mural thrombi and monocytes adhesion. These events may facilitate the release of growth factors or mitogenic factors, resulting in migration of smooth muscle cells from media into intima and excessive proliferation in intima.[1,7,13–17] We studied the extract of APN and FO in preventing stenosis and restenosis and their mechanisms.

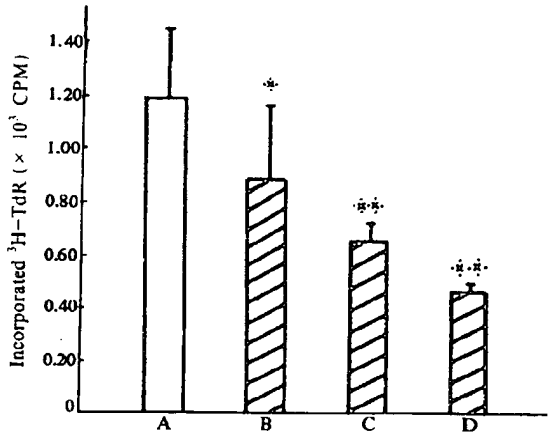

Fig 5. The in vitro inhibitory action of API_{0134} on the cultured fibroblast proliferation in the dose-dependent manner in the dose of 75μg / ml, 150μg / ml, and 300μg / ml. A. control (no API_{0134}), B, C, and D contained 75μg / ml, 150μg / ml and 300μg / ml of API_{0134}. * $P < 0.05$; * * $P < 0.01$.

The preliminary results showed that APN can significantly alleviate the severity of atherosclerotic iliac artery stenosis induced by deendothelialization and high cholesterol diet. Besides it may also markedly decrease the grade of restenosis after experimental angioplasty. Our previous studies on the human body and animals have proved that APN can significantly increase platelets cAMP and plasma PGI_2 concentration, decrease TXA_2 production, inhibit platelet aggregation and coronary thrombosis of dog induced by intimal damage.[18] However, these results are not confirmed in exploring the preventive effect on the occurrence of restenosis. Experiments should be done to study the mechanism. The effects of FO in preventing restenosis have been widely reported, but the results are controversial.[19,20] We thus take this drug as questionably positive control

drug.[19,20] Our experiments revealed that FO reduced the incidence and severity of iliac stenosis induced by high cholesterol diet and deendothelialization but the efficacy was not so significant as that of APN. In addition, local restenosis developed in all animals 4 weeks after angioplasty and fed by FO as demonstrated angiographically, but their severity was milder than the control group.

Monocytes play an important role in the pathogenesis of atherosclerosis and post-angioplasty restenosis. Once monocytes adhere to the artery wall, they will be transformed to macrophages and release mitogenic factors enhancing the migration of smooth muscle cells from arterial media to the intima and promoting their proliferation.[21,22] In vitro, blood monocytes may be transformed to macrophage and then may release growth factors after stimulation by Con A, which is 3–4.5 times potent incorporation with ^{3}H-TdR than that without Con A stimulation. Long-term feeding of APN or FO may remarkably inhibit monocytes to secrete growth factors or suppress their transformation. The effect of APN is more prominent than that of FO.

Cytosolic free Ca^{++} plays an extremely important role in morphologic change, secretory function, migration and proliferation of cells. Cytosolic $[Ca^{++}]i$ may combine with calmodulin to form Ca^{++}-calmodulin complex (Ca^{++}-Calm), which in turn bind the Ca^{++}-Calm dependent protein kinase to form active ternary complex triggering migration and proliferation of cells.[23,24] Experiments have shown that this process can be hindered by using calmodulin blocker or by inhibiting the increase of $[Ca^{++}]i$. Whereas $[Ca^{++}]i$ is found to be markedly increased prior to the migration and proliferation of smooth muscle cells.[25] Normally, the resting $[Ca^{++}]i$ is extremely low, and the transmembrane gradient is carried out chiefly by membrane Ca^{++}-ATPase.[23–25] In our experiment, we found that the activity of Ca^{++}-ATPase in atherosclerotic rabbit was markedly reduced. It was presumed that the derangement of Ca^{++} transmembranous transportation was affected by some deleterious factors or generation of excessive free radicals leading to the reduction of Ca^{++}-ATPase activity[26] and rising of $[Ca^{++}]i$, as well as triggering of migration and proliferation of smooth muscle cells with the development of consequent atherosclerosis. APN and FO, especially the former, may protect the Ca^{++}-ATPase activity of cell membrane from being reduced. This finding is consistent with the angiographic findings. Furthermore, the resting $[Ca^{++}]i$ was markedly decreased after treating with API_{0134} in vitro. The long-term feeding with APN in vivo may also lower the resting as well as thrombin-stimulated platelets $[Ca^{++}]i$. These findings lend us the theoretical ground in using APN to prevent the occurrence of restenosis.

Fibroblasts resembling smooth muscle cells have the same biological activity. They may multiply and proliferate in serum cultured media. The present study demonstrated the inhibitive effect of API_{0134} on the proliferation of fibroblast in dose dependent manner as proved by the concentration of ^{3}H-TdR incorporated into DNA. In the light of this finding, APN has provided a direct evidence in alleviating atherosclerosis and in preventing restenosis after angioplasty.

In summary, long-term feeding of APN may inhibit monocyte to secrete growth factors or mitogenic factors, prevent the reduction of membrane Ca^{++}-ATPase activity of atherosclerotic rabbit with consequent prevention of elevation of intracellular $[Ca^{++}]i$. In administering APN in vitro and vivo, the resting and thrombin-stimulated platelets $[Ca^{++}]i$ may be decreased, and the growth of fibroblast in dose dependent manner inhibited. These results suggest that APN may alleviate atherosclerosis after high cholesterol feeding and endothelial denudation and it is worth further studying in preventing the occurrence of restenosis after angioplasty. FO has the same but milder action, so it may be used as adjuvant measure for prevention of restenosis.

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Controlled Trial of Fish Oil for Regression of Human Coronary Atherosclerosis

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Objectives. **This randomized clinical trial tested whether fish oil supplements can improve human coronary atherosclerosis.**

Background. **Epidemiologic studies of populations whose intake of oily fish is high, as well as laboratory studies of the effects of the polyunsaturated fatty acids in fish oil, support the hypothesis that fish oil is antiatherogenic.**

Methods. **Patients with angiographically documented coronary heart disease and normal plasma lipid levels were randomized to receive either fish oil capsules (n = 31), containing 6 g of n-3 fatty acids, or olive oil capsules (n = 28) for an average duration of 28 months. Coronary atherosclerosis on angiography was quantified by computer-assisted image analysis.**

Results. **Mean (±SD) baseline characteristics were age 62 ± 7 years, plasma total cholesterol concentration 187 ± 31 mg/dl (4.83 ± 0.80 mmol/liter) and triglyceride levels 132 ± 70 mg/dl (1.51 ± 0.80 mmol/liter). Fish oil lowered triglyceride levels by 30% (p = 0.007) but had no significant effects on other plasma lipoprotein levels. At the end of the trial, eicosapentaenoic acid in adipose tissue samples was 0.91% in the fish oil group compared with 0.20% in the control group (p < 0.0001). At baseline, the minimal lumen diameter of coronary artery lesions (n = 305) was 1.64 ± 0.76 mm, and percent narrowing was 48 ± 14%. Mean minimal diameter of atherosclerotic coronary arteries decreased by 0.104 and 0.138 mm in the fish oil and control groups, respectively (p = 0.6 between groups), and percent stenosis increased by 2.4% and 2.6%, respectively (p = 0.8). Confidence intervals exclude improvement by fish oil treatment of >0.17 mm, or >2.6%.**

Conclusions. **Fish oil treatment for 2 years does not promote major favorable changes in the diameter of atherosclerotic coronary arteries.**

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Evidence from several lines of investigation suggests that n-3 polyunsaturated fatty acids may protect against atherosclerotic vascular disease. In arctic populations, low mortality from coronary heart disease is attributed to a diet that is rich in oily fish (1). In a controlled trial in British patients with coronary heart disease, intake of fatty fish significantly reduced coronary heart disease death (2). The protective effect of fish intake could be caused by the fish oil (3,4), by other nutrients in fish or by an indirect effect of fish intake on other aspects of the diet. The n-3 polyunsaturated long-chain fatty acids unique to fish oils demonstrate several biologic effects that could be antiatherogenic, including arterial vasodilation (5,6), reduced thromboxane and enhanced prostacyclin synthesis (3,4), inhibition of platelet aggregation (3,4), decreased blood pressure (7), reduction of plasma triglyceride levels (8) and elevation of high density lipoprotein $(HDL)_2$ cholesterol (9,10). However, other effects of n-3 fatty acids may have a proatherogenic effect, including elevations of plasma low density lipoprotein (LDL) cholesterol (9,11,12) and glucose levels (13) and enhanced oxidation of LDL cholesterol (14,15). In several animal models of atherosclerosis, fish oil diminished atherogenesis (16–22), but other studies have found no effect (15,23,24) or even worsening (25–27). Studies of fish oil in human coronary atherosclerosis have been limited to attempts to prevent restenosis after coronary angioplasty, and results have been mixed (28,29). Therefore, to date, the value of n-3 fatty acids as agents for prevention or treatment of human atherosclerosis remains undetermined. In the present study, in patients with coronary artery disease, we tested the effect of a moderate dose of fish oil on atherosclerosis in native coronary arteries.

Methods

Patients. Eligible patients had narrowing of ≥30% lumen diameter of a major coronary artery, as shown by diagnostic coronary angiography at either Brigham and Women's or Beth Israel Hospitals, a total cholesterol concentraation <250 mg/dl (6.43 mmol/liter) and triglyceride level <350 mg/dl (4.0 mmol/

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liter) and were between the ages of 30 and 75 years. Patients were determined to be eligible by lipid criteria from measurements on two qualifying visits conducted 1 to 2 weeks apart. Qualifying visits were delayed at least 8 weeks after hospital discharge for patients who had acute myocardial infarction and at least 12 weeks for patients who underwent coronary artery bypass surgery or angioplasty. Patients with congestive heart failure; liver, renal or serious gastrointestinal disease; insulin-dependent diabetes mellitus; current cigarette smoking; or alcohol intake >14 drinks/week were excluded. Randomization of patients was stratified according to clinical management of their coronary artery disease (medical or surgical) and total/HDL cholesterol ratio (>6.0 or ≤6.0). Forty-one of 80 patients were randomized to the fish oil group and 39 to the control group. The study was approved by the Institutional Review Boards of Brigham and Women's and Beth Israel Hospitals, and written informed consent was obtained at the first qualifying visit and again before the follow-up coronary catheterization.

During the initial hospital stay for coronary catheterization, dietary instruction was provided to every patient according to the guidelines of the National Cholesterol Education Program Step I (30). The instruction was reinforced, and a 7-day diet record was collected at the randomization visit and every 3 months during the trial. The diet records were analyzed using a computerized nutrient data base (Food Processor II, ESHA Research).

Protocol. Patients in the fish oil group were given bottles containing a 3-month supply of fish oil capsules (Promega, Parke-Davis). They were instructed to take twelve 1-g capsules daily, in divided doses, preferably after meals. Each fish oil capsule contained 500 mg of n-3 polyunsaturated fatty acids composed of eicosapentaenoic acid (240 mg), docosahexaenoic acid (160 mg) and other (100 mg) (mainly docosapentaenoic acid). Therefore, the total daily dose of n-3 fatty acids was 6 g. The control group was treated similarly with capsules of olive oil that were identical in appearance to the fish oil capsules. The patients and personnel responsible for laboratory measurements, cardiac catheterization, and analysis of angiography films were blinded to treatment assignment.

Every 12 weeks, a research nurse reviewed with the patients side effects, diet, and concomitant medications and performed a pill count. Every 24 weeks, the patients received an interval medical history and physical examination by a physician. At the 12- and 24-week visits and every 24 weeks thereafter, a fasting blood sample was obtained for lipid analysis. At the end of the study, a sample of adipose tissue was aspirated from gluteal fat for fatty acid measurements.

If the total cholesterol level of any patient increased to ≥250 mg/dl (6.43 mmol/liter) on two consecutive measurements, intensified dietary instruction was given, followed by drug therapy with cholestyramine 4 to 16 g or nicotinic acid 2 g, or both, as needed to lower total cholesterol to <250 mg/dl (6.43 mmol/liter).

Lipid measurements. Plasma lipids were measured on fasting fresh plasma at the Lipid Research Laboratory, Brigham and Women's Hospital. Cholesterol and triglyceride levels were measured by enzymatic reagents (Boehringer Mannheim) in whole plasma (31). The HDL cholesterol was measured in plasma after precipitation of very low density lipoprotein (VLDL) and LDL cholesterol by dextran and magnesium chloride (32). The LDL cholesterol was calculated. The fatty acid composition of adipose tissue was determined by capillary gas chromatography (33). Apolipoprotein B was measured by immunonephelometry (Inkstar Corp.) in one batch on samples continuously stored at −80°C using calibrators provided by the Centers for Disease Control. Lipoprotein Lp(a) was measured by sandwich enzyme-linked immunosorbent assay (Terumo, Inc.).

Cardiac catheterization. At the baseline cardiac catheterization, the following conditions were recorded and reproduced at the time of the repeat procedure: cine camera angle and skew, contrast agent (ionic or nonionic), sequence of angiographic views and the dosing of vasoactive medications. To confirm reproduction of angiographic views, the initial cine film was viewed on a projector in the catheterization laboratory during the repeat procedure. On hospital admission on the day before the angiography, the patients were treated with the same cardiac medications they were taking at the time of the initial procedure unless contraindicated for medical reasons. The two catheterizations were performed at the same time of day whenever possible to eliminate any diurnal variation in vasomotor tone.

Quantitative angiography. From films unlabeled as to treatment assignment, coronary artery lumen diameter was quantitated by an operator-interactive program as previously described (34). The classification of segments was similar to that used in other trials (35). Lesions were defined as lumen obstructions >20%. New lesions were defined as vessels with an obstruction <20% at the time of initial catheterization, ≥20% at follow-up examination and a change ≥7.8% diameter stenosis, previously determined to be significant (34). For vessels without a lesion, segments >2.0 mm, were analyzed. Lesions that underwent angioplasty and adjacent vessel segments were not analyzed. Five consecutive frames from the same phase of the cardiac cycle (preferably end-diastole) were analyzed by edge detection (36,37) after threefold to fourfold optical magnification and digitization into a 512 × 512-pixel array. The minimal diameter of a stenosis was defined as the minimal diameter of a polynomial fit to the five pixels surrounding the minimal point of the diameter–length relation.

Statistics. The primary outcome variable was the change in minimal diameter of coronary artery lesions expressed as a continuous variable. The individual coronary artery lesions comprised the basic units in the analysis. Unbypassed and bypassed vessel segments were included as in a previous trial (38). The treatment effect was adjusted by multiple logistic regression for the intraclass correlation between changes in lesions in a person (39); the initial diameter of the lesions, because initial diameter has been shown to be a significant predictor of lesion change (40); and the differences between the groups in the proportion of bypassed and unbypassed

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Table 1. Baseline Characteristics of 59 Study Patients

	Fish Oil Group (n = 31)	Control Group (n = 28)
Age (yr)	62 ± 7	62 ± 7
Duration in trial (days)	829 ± 127	890 ± 123
Duration from initial to final cardiac catheterization	958 ± 136	993 ± 96
Gender (M/F)	29/2	26/2
Hypertension	15 (48%)	10 (36%)
Diabetes	5 (16%)	3 (11%)
Family history of CVD	21 (68%)	13 (46%)
CABG	16 (52%)	12 (43%)
MI	17 (55%)	16 (57%)
Medication		
Beta-blockers	17 (55%)	15 (54%)
Calcium channel blockers	16 (52%)	12 (43%)
Nitrates	13 (42%)	7 (25%)
Antiplatelet agents	30 (97%)	26 (93%)
ACE inhibitors	3 (10%)	3 (11%)
Oral hypoglycemic drugs	5 (16%)	1 (4%)

Data presented are mean value ± SD or number (%) of patients. ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft surgery; CVD = cardiovascular disease; F = female; M = male; MI = myocardial infarction.

lesions. The effects of covariates, such as age, baseline plasma lipid levels and change in lipids, were also studied. Patient-specific changes were derived using the mean of the changes in diameter of the lesions in each patient.

Results

Patients. The final study group consisted of the 59 patients who underwent follow-up cardiac catheterization (55 men, 4 women; 31 patients in the fish oil group, 28 in the control group) (Table 1). Twenty-one randomized patients did not complete the protocol (10 in the fish oil, 11 in the control group). Reasons for not completing the study were death (one in the control group); refusal to undergo the second cardiac catheterization (three in the fish oil group, nine in the control group); development of medical conditions precluding participation (three in the fish oil group, one in the control group); intolerance to the capsules (three in the fish oil group); and a missing initial angiography film (one in the fish oil group).

There were no significant differences in the baseline characteristics of the patients between the two treatment groups (Tables 1 and 2). Dietary saturated fat comprised 8 ± 2% (mean ± SD) of energy intake in both groups at baseline and during follow-up. Dietary cholesterol intake, ~200 ± 90 mg/day at baseline, decreased in the fish oil group by 28 mg compared with an increase in the control group of 22 mg ($p = 0.04$). Both groups gained a mean of 2 kg body weight during the trial ($p < 0.005$). Adherence, estimated by pill counts, averaged 80% in the fish oil group and 90% in the control group. Medication use was similar among the groups at baseline except for oral hypoglycemic drugs (Table 1), and there were no significant changes in medication use during the trial in either group.

Plasma lipoprotein changes. As a group, the patients had average levels at baseline, and there were no significant differences between the fish oil and control groups (Table 2). Plasma triglyceride levels decreased by 30% in the fish oil group compared with those in the control group ($p = 0.007$). The decrease in triglyceride levels in the fish oil group was established by 12 weeks and remained stable throughout the follow-up. There were no significant differences between the groups in changes in plasma total, LDL or HDL cholesterol or apolipoprotein B or lipoprotein Lp(a) levels. Hypocholesterolemic drug therapy for a total cholesterol level >250 mg/dl (6.43 mmol/liter) was required for four patients in the fish oil group and none in the control group. The medications used were cholestyramine (4 to 8 g/day) in three patients and cholestyramine (8 to 16 g) with nicotinic acid (2 g) in one patient.

Adipose tissue fatty acids. At the end of the trial, adipose tissue in the fish oil group was significantly enriched in the n-3 polyunsaturated fatty acids of marine origin that were contained in the fish oil ($p < 0.0001$) (Table 3). In contrast, the control group that received olive oil had a significantly higher content of oleic acid ($p = 0.0009$), the major fatty acid in olive oil, and higher levels of palmitic acid ($p = 0.05$), the major

Table 2. Body Weight and Plasma Lipid Levels at Baseline and During Fish Oil or Control Supplementation

	Fish Oil Group (n = 31)			Control Group (n = 28)		
	Baseline	Follow-Up	Difference	Baseline	Follow-Up	Difference
Body weight (kg)	80 ± 14	82 ± 14	2 ± 3*	79 ± 15	80 ± 15	2 ± 3*
Systolic BP (mm Hg)	126 ± 29	129 ± 16	3 ± 29	133 ± 19	137 ± 29	5 ± 25
Diastolic BP (mm Hg)	76 ± 16	77 ± 7	1 ± 18	77 ± 7.6	77 ± 7	0 ± 8
Cholesterol (mg/dl)	189 ± 33	194 ± 37	5 ± 17	184 ± 28	193 ± 24	9 ± 20†
HDL-C (mg/dl)	41 ± 9	42 ± 11	1 ± 6	40 ± 12	42 ± 13	3 ± 7
LDL-C (mg/dl)	122 ± 29	132 ± 30	10 ± 17*	117 ± 27	122 ± 24	6 ± 17
Triglycerides (mg/dl)	128 ± 67	101 ± 50	−28 ± 53*	137 ± 73	143 ± 67	6 ± 35‡
Apolipoprotein B (mg/dl)	80 ± 13	86 ± 15	6 ± 6*	74 ± 16	79 ± 13	5 ± 9*
Lipoprotein Lp(a) (mg/dl)	8.2 ± 4.4	9.7 ± 5.1	1.2 ± 2.8†	6.4 ± 3.6	5.7 ± 3.9	−1.1 ± 7.2

*$p < 0.01$, †$p < 0.05$ for within-group changes. ‡$p < 0.01$ for between-group changes. All differences between baseline values were not significant ($p > 0.1$). Data presented are mean value ± SD, except those for lipoprotein Lp(a), which are geometric mean values. BP = blood pressure; HDL-C (LDL-C) high (low) density lipoprotein cholesterol.

Table 3. Adipose Tissue Fatty Acid Levels (mean ± SD) After 2.4 Years of Fish Oil or Control Supplementation

Acid	Fish Oil Group (n = 29)	Control Group (n = 28)	p Value
Lauric	0.74 ± 0.57	0.86 ± 0.43	0.4
Palmitic	12.4 ± 3.7	14.1 ± 2.5	0.048
Stearic	3.37 ± 0.85	3.0 ± 0.9	0.16
Oleic	37.3 ± 6.6	42.3 ± 3.9	0.0009
Linoleic	18.2 ± 4.7	18.7 ± 3.7	0.7
Arachidonic	0.60 ± 0.28	0.89 ± 0.37	0.001
EPA (n-3)	0.91 ± 0.53	0.20 ± 0.31	< 0.0001
DPA (n-3)	0.62 ± 0.25	0.25 ± 0.15	< 0.0001
DHA (n-3)	0.84 ± 0.41	0.31 ± 0.23	< 0.0001
EPA + DPA + DHA	2.37 ± 1.14	0.76 ± 0.66	< 0.0001

Two patients refused the fat biopsy. DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid.

tissue saturated fatty acid. Arachidonic acid was lower in the fish oil group than in the control group (p = 0.001).

Coronary artery lesions. The principal analysis consists of 179 lesions in 31 patients in the active group (5.8 lesions/patient) and 126 lesions in 28 patients in the control group (4.5 lesions/patient) (Table 4, Fig. 1). The difference in number of lesions is mainly accounted for by a greater number of bypassed vessels in the fish oil group, by chance. The adjusted changes were 0.104 and −0.138 mm in minimal diameter (p = 0.6) and +2.4% and +2.6% in percent diameter narrowing (p = 0.8) in the fish oil and control groups, respectively, indicating slight worsening in both groups (Table 4, Fig. 1). The adjusted differences between the groups were +0.03 mm (95% confidence interval [CI] −0.10 to 0.17 mm) and −0.2% (95% CI −2.6 to 2.1%). These confidence intervals indicate that the trial excludes improvement by fish oil treatment of >0.17 mm, or >2.6% stenosis. Lesions in unbypassed vessels showed less change in minimal diameter than lesions that were in bypassed circulation (p < 0.0001), but there were no significant differences between the treatment groups. In contrast, the diameter of normal vessel segments increased in the fish oil group but not in the control group (p = 0.03 between groups for minimal diameter; p = 0.07 for average diameter).

Additional analyses of lesion change. Patient-specific analysis of the changes in coronary lesions revealed no significant differences between the groups; for all lesions, mean change was −0.12 (SD 0.29) and −0.11 (SD 0.27) in the fish oil and control groups, respectively (p = 0.9), and for unbypassed lesions the changes were −0.10 (SD 0.29) and −0.11 (SD 0.34) (p = 0.9). For a categoric analysis, lesions were classified as progressing or regressing if the changes were ≥7.8% in percent stenosis as previously determined (34). The majority of the lesions showed no change (Table 5), and there were no significant differences between the groups. Restricting the

Table 4. Effect of Fish Oil on Coronary Artery Disease: Lesion-Specific Analysis

	Fish Oil Group				Control Group				
	No. of Lesions	Pre	Post	Adjusted Change	No. of Lesions	Pre	Post	Adjusted Change	Fish Oil − Control
All abnormal segments									
Min diam (mm)	179	1.74 ± 0.82	1.62 ± 0.86	−0.104 ± 0.05	126	1.57 ± 0.71	1.46 ± 0.67	−0.138 ± 0.04*	0.03 (−0.10–0.17)
Stenosis (%)		46.5 ± 14.2	49.4 ± 12.5	2.4 ± 0.7*		48.7 ± 13.7	50.7 ± 12.2	2.6 ± 0.8*	−0.2 (−2.6–2.1)
Unbypassed abnormal segments									
Min diam (mm)	96	1.85 ± 0.85	1.82 ± 0.94	−0.06 ± 0.07	86	1.64 ± 0.71	1.55 ± 0.70	−0.10 ± 0.04	0.04 (−0.14–0.23)
Stenosis (%)		43.8 ± 13.5	46.9 ± 11.7	2.9 ± 1.3†		46.7 ± 12.8	49.2 ± 12.0	3.2 ± 1.1†	−0.3 (−3.8–3.2)
Bypassed abnormal segments									
Min diam (mm)	83	1.61 ± 0.76	1.39 ± 0.70	−0.23 ± 0.06*	40	1.43 ± 0.70	1.28 ± 0.54	−0.23 ± 0.06*	0.00 (−0.16–0.17)
Stenosis (%)		49.7 ± 14.3	52.4 ± 12.8	2.3 ± 1.1†		53.1 ± 14.5	53.8 ± 12.3	1.7 ± 1.4	0.6 (3.0–4.2)
Unbypassed normal segments									
Min diam (mm)	41	2.24 ± 0.96	2.38 ± 0.98	0.15 ± 0.07†	51	2.40 ± 0.92	2.33 ± 0.90	−0.05 ± 0.05	0.20 (0.01–0.39) (p = 0.03)
Av diam (mm)		2.73 ± 0.94	2.90 ± 0.97	0.17 ± 0.07†		2.98 ± 0.93	2.97 ± 0.98	−0.01 ± 0.07	0.19 (−0.03–0.40)

*p < 0.01, †p < 0.05 for within-group changes. Adjusted changes were computed by multiple regression analysis with adjustment for the intraclass correlation, differences in pretreatment value (Pre) and proportion of bypassed lesions. Data presented are mean values ± SD (for pretreatment and posttreatment [Post] values) or ±SE (for adjusted change). Av (Min) diam = average (minimal) diameter; Fish Oil − Control = difference between adjusted changes (95% confidence intervals).

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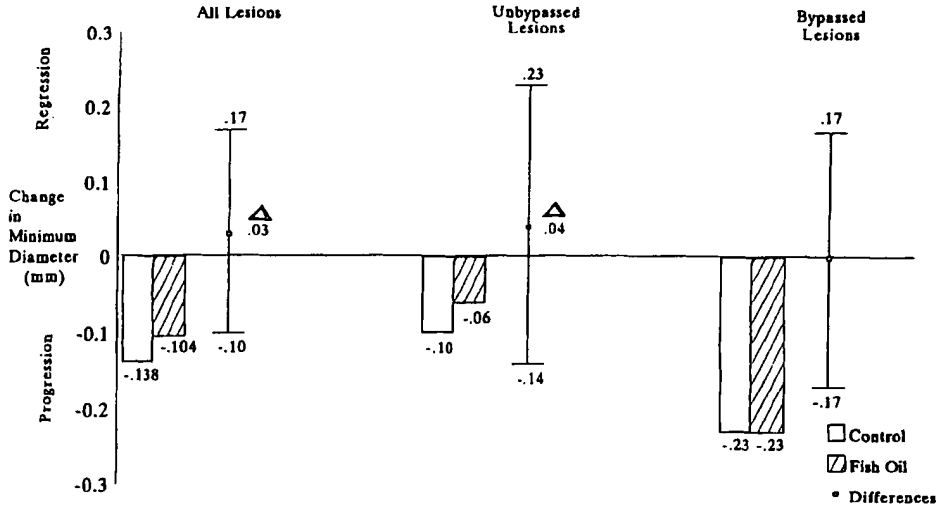

Figure 1. Changes in coronary artery lesions before and after 2.4 years of treatment with fish oil. The between-group differences are shown with 95% confidence intervals (**vertical lines**). Changes in minimal coronary artery diameter and percent stenosis in the active treatment and control groups were adjusted for the effects of differences in pretreatment values, for differences in the proportion of lesions that were in a bypassed circulation and for the intraclass correlation of the changes in lesions within a patient. Change = post-treatment minus pretreatment.

categoric analysis to unbypassed lesions produced similar results to the full group. One unbypassed vessel became occluded in the fish oil group compared with three vessels in three patients in the control group.

Subgroup analyses did not demonstrate any significant effect of fish oil in patients according to baseline lipid levels, change in lipid levels, baseline coronary lesion diameter or adipose tissue n-3 fatty acid levels.

Clinical coronary disease events are counted for all randomized patients up to the time of repeat catheterization or for 2.4 years in the dropouts. In the fish oil group, there were eight events in seven patients (one nonfatal myocardial infarction, one stroke, three coronary angioplasties, three hospital admissions for unstable angina). In the control group, there were 11 events in seven patients (1 coronary death, 2 nonfatal myocardial infarctions, 1 hospital admission for congestive heart failure, 3 coronary angioplasties, 4 hospital admissions for unstable angina). No patient had coronary bypass surgery after randomization.

Discussion

The present study found no evidence that the progression of coronary atherosclerosis over a 2.4-year period, as measured by change in lumen diameter, is affected by fish oil supplementation. The patients were proved to be compliant by the findings of a sustained decrease in plasma triglyceride levels in the fish oil group and the substantially higher n-3 fatty acid levels in adipose tissue biopsy samples. The equilibration time for dietary and adipose tissue fatty acid is ~2 years (41). We expect that the n-3 fatty acids enriched the patients' coronary lesions, as found in a previous pathologic study (42).

Limitations of the study. The confidence intervals of the differences between the groups exclude beneficial effects of >0.17 mm in minimal coronary diameter or >2.6% stenosis. This finding indicates that if fish oil were to have had a favorable effect of magnitude similar to that reported with hypocholesterolemic drug therapy or with nonpharmacologic therapy (35,43–46), then such a difference would have been detectable in the present study. This sensitivity is the result of there being 305 lesions available for analysis, the precision of the angiographic measurements and the highly powered statistical analysis technique. However, it is possible that fish oil could produce very small improvement in coronary diameter, perhaps 0.04 mm as in a recent trial of lovastatin (47), that would not have been detected in our trial. Our trial experienced a dropout rate of 26% compared with 10% to 26% in previous trials of similar duration (35,38,44,45,47). The sever-

Table 5. Effect of Fish Oil on Progression, Regression, New Lesions and Total Occlusions

	Fish Oil Group		Control Group	
	No. (%) of Patients (n = 31)	No. (%) of Lesions (n = 179)	No. (%) of Patients (n = 28)	No. (%) of Lesions (n = 126)
Progression*	11 (35%)	52 (29%)	12 (43%)	24 (19%)
Regression	4 (13%)	23 (13%)	7 (25%)	20 (16%)
Mixed	14 (45%)	—	6 (21%)	—
Total occlusions	6 (19%)	12 (7%)	6 (21%)	9 (7%)
No changes	2 (6%)	101 (51%)	3 (11%)	78 (62%)
New lesions	2 (6%)	3 (2%)	4 (14%)	4 (3%)

*Total occlusions not included.

ity of coronary disease in the present trial is similar to or worse than that of previous studies (35,38,43–47). Previous studies conflict as to whether mild or severe lesions are benefited by therapy (45,47). Finally, although the duration of the treatment, 28 months, is similar to (35,38,45,47) or longer than (43,46) previous regression trials, we cannot exclude the possibility that fish oil could produce benefit that is too gradual to be detected or that is preceded by a latent period of ≥2 years.

Potential biologic causes of lack of benefit. 1) The olive oil that the control group received for a placebo could have been beneficial, for example, by improving serum lipids (48). This seems to be unlikely, because no lipid-lowering effect was evident in our patients in the control group, and the control group showed progression of disease at a comparable extent to that in the control groups in other arteriographic trials. 2) Fish oil could have a proatherosclerotic action because the highly unsaturated fatty acids appear to increase the susceptibility of LDL for oxidation (14,15), an event that enhances the atherogenicity of LDL in cultured cells. However, the net effect of fish oil on LDL oxidation in vivo is not certain because laboratory studies found potentially beneficial counterbalancing actions of fish oil, including protection from atherogenic effects of oxidized LDL (49), diminished production of superoxide by monocytes (50), prevention of lipid peroxidation by platelets (51) and stimulation of alpha-tocopherol incorporation into cell membranes (52).

We found that the diameter of normal coronary arteries increased in the fish oil but not in the control group, a finding of borderline significance ($p = 0.07$ for average diameter; $p = 0.04$ for minimal diameter). Because the change in normal arteries was not a primary end point, this could be caused by chance in view of multiple statistical comparisons. However, it is possible that fish oil promoted vasodilation in these arteries or improved their endothelial function (3–6).

Patients with normal plasma lipid levels were studied because hypocholesterolemic drug treatment has been recommended for hyperlipidemic patients. In this normolipidemic group, the possibility that coronary atherosclerosis might be less dependent on plasma cholesterol levels made fish oil an attractive intervention because the mechanism of action could be independent of the effects on plasma lipid levels (2,3,16,21,22). In our patients, the mean plasma cholesterol level, 187 mg/dl (4.83 mmol/liter), is by far the lowest of any human atherosclerosis regression trial. Despite our patients' low cholesterol levels, the coronary lesions in the fish oil and control groups progressed at a similar rate as in hyperlipidemic patients in certain previous studies. In both groups, the progression of lesions was not correlated with plasma lipid levels, indicating that in this population, nonlipid risk factors may regulate the atherosclerotic process.

Conclusions. Epidemiologic and intervention studies do not reveal a clear picture of the effects of fish oil on coronary atherosclerosis. Arctic peoples consume marine oils in fish and sea mammals and have low rates of coronary heart disease (1). Certain observational studies in industrialized countries have found a protective association of fish intake on the development of coronary heart disease (53–55), but other studies have not (56–59). However, fish intake is much lower in these countries than in the arctic. Restenosis after coronary angioplasty is not convincingly benefited despite multiple studies (28,29,60). The most compelling evidence in favor of fish is a clinical trial of patients who had coronary heart disease (2). Patients were asked to ingest two portions per week of fatty fish, which supplied ~0.5 mg of n-3 fatty acids daily, one-twelfth of the dose in our trial. Death and recurrent nonfatal coronary heart disease were lowered early in the 5-year follow-up period in the fish group compared with that in the control group. It is possible that fish oil could prevent coronary events by retarding thrombosis or improving endothelial function that leaves coronary stenosis unchanged or by preventing fatal ventricular arrhythmias (61). Alternatively, the relatively low quantity of n-3 fatty acids consumed in the previous trial (2) raises a question about the effect of fish oil itself and supports the possibility that other constituents of the fish are cardioprotective. In view of these uncertainties, a definitive assessment of the effect of fish oil on coronary heart disease requires a sufficient number of patients to determine whether myocardial infarction and death rates are reduced.

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Spontaneous regression of restenosis: an angiographic study.

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OBJECTIVES. This study was designed to examine the possibility that spontaneous regression in stenosis severity occurs over time in patients with restenosis after percutaneous transluminal coronary angioplasty. BACKGROUND. The underlying mechanisms of restenosis are intimal hyperplasia and smooth muscle cell proliferation in response to vascular injury. We hypothesized that the initial hyperplastic response is followed by dynamic remodeling and eventual spontaneous regression, leading to stabilization or a reduction in stenosis severity. METHODS. A total of 136 patients participated in a trial to evaluate the efficacy of fish oil versus placebo in preventing restenosis after angioplasty. One hundred thirteen patients completed this study with angiographic follow-up, of whom 56 had restenosis. Of these, 19 were asymptomatic and did not undergo repeat revascularization; 15 consented in a separate study to undergo repeat angiography, which was performed 6 to 25 months later to assess the possibility of regression. RESULTS. There was a significant mean (+/- SD) decrease in lesion severity from 66.9 +/- 8.7% to 47.5 +/- 9.0% ($p < 0.0001$) and a significant mean increase in minimal lumen diameter from 0.91 +/- 0.31 mm to 1.44 +/- 0.35 mm ($p < 0.0001$). No patient showed progression of stenosis, but regression of restenosis, defined as a decrease in minimal lumen diameter > or = 0.2 mm, was noted in 12 of the patients. CONCLUSIONS. Although all 15 study patients were asymptomatic, similar changes may occur in symptomatic patients. A trial of medical therapy may be appropriate in asymptomatic or mildly symptomatic patients before further interventions. This strategy would avoid unnecessary invasive procedures, prevent a "restenosis cycle" and result in significant cost

savings.

Publication Types:
- Clinical Trial
- Controlled Clinical Trial
- Multicenter Study

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☐ 1: J Am Coll Cardiol 1995 Jun;25(7):1492-8 Related Articles, NEW Books, LinkOut

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group.

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OBJECTIVES. This randomized clinical trial tested whether fish oil supplements can improve human coronary atherosclerosis. BACKGROUND. Epidemiologic studies of populations whose intake of oily fish is high, as well as laboratory studies of the effects of the polyunsaturated fatty acids in fish oil, support the hypothesis that fish oil is antiatherogenic. METHODS. Patients with angiographically documented coronary heart disease and normal plasma lipid levels were randomized to receive either fish oil capsules (n = 31), containing 6 g of n-3 fatty acids, or olive oil capsules (n = 28) for an average duration of 28 months. Coronary atherosclerosis on angiography was quantified by computer-assisted image analysis. RESULTS. Mean (+/- SD) baseline characteristics were age 62 +/- 7 years, plasma total cholesterol concentration 187 +/- 31 mg/dl (4.83 +/- 0.80 mmol/liter) and triglyceride levels 132 +/- 70 mg/dl (1.51 +/- 0.80 mmol/liter). Fish oil lowered triglyceride levels by 30% ($p = 0.007$) but had no significant effects on other plasma lipoprotein levels. At the end of the trial, eicosapentaenoic acid in adipose tissue samples was 0.91% in the fish oil group compared with 0.20% in the control group ($p < 0.0001$). At baseline, the minimal lumen diameter of coronary artery lesions (n = 305) was 1.64 +/- 0.76 mm, and percent narrowing was 48 +/- 14%. Mean minimal diameter of atherosclerotic coronary arteries decreased by 0.104 and 0.138 mm in the fish oil and control groups, respectively ($p = 0.6$ between groups), and percent stenosis increased by 2.4% and 2.6%, respectively ($p = 0.8$). Confidence intervals exclude improvement by fish oil treatment of > 0.17 mm, or > 2.6%. CONCLUSIONS. Fish oil treatment for 2 years does not promote major favorable changes in the diameter of atherosclerotic coronary arteries.

Publication Types:

Pt left 1-17-02 fish oil stenosis

☐ 1: Chin Med J (Engl) 1994 Jun;107(6):464-70 Related Articles, NEW Books

Prevention of atherosclerotic arterial stenosis and restenosis after angioplasty with Andrographis paniculata nees and fish oil. Experimental studies of effects and mechanisms.

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Restenosis rate after coronary angioplasty has been up to 30%-40%. To solve this problem, we studied the effects of Andrographis Paniculata Nees (APN) and fish oil (FO, omega 3 polyunsaturated fatty acids over 70%) on atherosclerotic stenosis and restenosis after experimental angioplasty and the relevant mechanisms of APN and FO. Preliminary results showed that APN can significantly alleviate atherosclerotic iliac artery stenosis induced by both deendothelialization and high cholesterol diet (HCD) and restenosis following angioplasty in rabbits. FO showed the same but milder effects than APN did. Both APN and FO significantly inhibited blood monocytes to secrete growth factors in vivo. Ca(++)-ATPase activity of cell membrane of atherosclerotic rabbits was significantly decreased, while APN or FO, especially the former alleviated this reduction. Refined extract of APN significantly decreased in vitro resting platelet [Ca++]i and in vivo the resting and thrombin-stimulated platelet [Ca++]i after oral administration of APN for 2 weeks. APN significantly inhibited cell growth or DNA synthesis in dose-dependent manner. In conclusion because of the mechanisms described above, APN can alleviate atherosclerotic artery stenosis induced by both deendothelialization and HCD as well as lower restenosis rate after experimental angioplasty. The effects of APN are evidently superior to those of FO.

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- Lancet. 1992 May 16;339(8803):1241; discussion 1242.
- Lancet. 1992 May 16;339(8803):1241; discussion 1242.
- Lancet. 1992 May 16;339(8803):1241; discussion 1242.
- Lancet. 1992 May 16;339(8803):1243.

Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS)

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To assess the effect of dietary reduction of plasma cholesterol concentrations on coronary atherosclerosis, we set up a randomised, controlled, end-point-blinded trial based on quantitative image analysis of coronary angiograms in patients with angina or past myocardial infarction. Another intervention group received diet and cholestyramine, to determine the effect of a greater reduction in circulating cholesterol concentrations. 90 men with coronary heart disease (CHD), who had a mean (SD) plasma cholesterol of 7.23 (0.77) mmol/l were randomised to receive usual care (U, controls), dietary intervention (D), or diet plus cholestyramine (DC), with angiography at baseline and at 39 (SD 3.5) months. Mean plasma cholesterol during the trial period was 6.93 (U), 6.17 (D), and 5.56 (DC) mmol/l. The proportion of patients who showed overall progression of coronary narrowing was significantly reduced by both interventions (U 46%, D 15%, DC 12%), whereas the proportion who showed an increase in luminal diameter rose significantly (U 4%, D 38%, DC 33%). The mean absolute width of the coronary segments (MAWS) studied decreased by 0.201 mm in controls, increased by 0.003 mm in group D, and increased by 0.103 mm in group DC (p less than 0.05), with improvement also seen in the minimum width of segments, percentage diameter stenosis, and edge-irregularity index in intervention groups. The change in MAWS was independently and significantly correlated with LDL cholesterol

concentration and LDL/HDL cholesterol ratio during the trial period. Both interventions significantly reduced the frequency of total cardiovascular events. Dietary change alone retarded overall progression and increased overall regression of coronary artery disease, and diet plus cholestyramine was additionally associated with a net increase in coronary lumen diameter. These findings support the use of a lipid-lowering diet, and if necessary of appropriate drug treatment, in men with CHD who have even mildly raised serum cholesterol concentrations.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

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Reversibility of fixed atherosclerotic lesions with aggressive risk factor modification.

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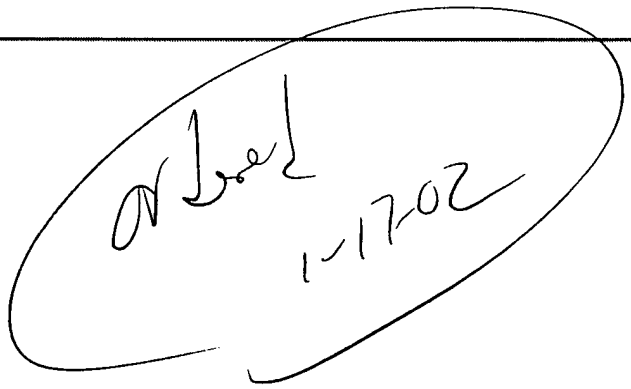
Seven patients with atherosclerotic coronary artery disease documented by coronary angiography and exercise stress testing were treated with the American Heart Association Step II Diet, a walking program, and combination drug therapy with niacin, cholestyramine, gemfibrozil, and/or lovastatin. As a result of this intervention, there was a mean weight loss of 24.7 pounds, a mean reduction in cholesterol from 297 mg% to 167 mg%, a mean increase in high density lipoprotein cholesterol from 33 mg% to 55 mg%, and a mean reduction in triglyceride levels from 248 mg% to 58 mg%. Repeat exercise stress testing and coronary angiography were performed 2 years after the initial catheterization. Photographs of end-diastolic frames were compared utilizing the same views with the same magnification. In six of the seven patients, there was a mean increase in luminal area at the greatest stenosis of 1.3 mm2 in eight lesions present at initial catheterization. In four of these six patients, there was evidence for improvement in coronary blood flow manifested by improvement in electrocardiogram (ECG) exercise stress testing and/or exercise thallium stress testing. In one patient, there was a mean decrease in luminal area at greatest stenosis of 1.35 mm2 in two lesions and the development of an additional plaque in an area which was previously normal. In addition, this patient had evidence for progression by ECG exercise stress testing. Aggressive risk factor modification can reverse what were previously considered "fixed" atherosclerotic lesions in selected patients.

PMID: 1956536 [PubMed - indexed for MEDLINE]



combined diet + medical tx

13: JAMA 1990 Dec 19;264(23):3007-12 Related Articles, NEW Books, LinkOut

Comment in:
- JAMA. 1991 Apr 3;265(13):1688-9.

Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens.

Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ.

Cardiovascular Research Institute, University of California, San Francisco 94143-0130.

We conducted a randomized, controlled trial in 72 patients with heterozygous familial hypercholesterolemia to test whether reducing plasma low-density lipoprotein levels by diet and combined drug regimens can induce regression of coronary lesions. Four hundred fifty-seven lesions were measured before and after a 26-month interval by computer-based quantitative angiography. The primary outcome variable was within-patient mean change in percent area stenosis. Mean low-density lipoprotein cholesterol levels decreased from 7.32 +/- 1.5 to 4.45 +/- 1.6 mmol/L. The mean change in percent area stenosis among controls was +0.80, indicating progression, while the mean change for the treatment group was -1.53, indicating regression (P = .039 by two-tailed t test for the difference between groups). Regression among women, analyzed separately, was also significant. The change in percent area stenosis was correlated with low-density lipoprotein levels on trial. We conclude that reduction of low-density lipoprotein cholesterol levels can induce regression of atherosclerotic lesions of the coronary arteries in patients with familial hypercholesterolemia. The anticipation of benefit from treatment applies to women and men alike.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 2243428 [PubMed - indexed for MEDLINE]

Ordered 1-17-02

ASA + Stenosis of Brain (1-17-02

☐ **1:** J Neurol Sci 1995 Mar;129(1):76-7 Related Articles, NEW **Books**, LinkOut

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Carotid endarterectomy for patients with asymptomatic internal carotid artery stenosis. National Institute of Neurological Disorders and Stroke.

On September 28, 1994, the investigators of the Asymptomatic Carotid Atherosclerosis Study (ACAS) reported the interim results of a randomized controlled clinical trial of carotid endarterectomy in patients who have asymptomatic carotid stenosis of greater than 60% reduction in diameter. In addition to aspirin and aggressive management of modifiable risk factors, one-half of the patients were randomly assigned to receive surgery after angiographic confirmation of the lesion. Carotid endarterectomy is beneficial with a statistically significant absolute reduction of 5.8% in the risk of the primary end point of stroke within 5 years and a relative risk reduction of 55%. As a consequence of the trial reaching statistical significance in favor of endarterectomy, and on the recommendation of the study's data monitoring committee, physicians participating in the study were immediately notified and advised to reevaluate patients who did not receive surgery. It is important to note that the success of the operation is dependent on medical centers and surgeons who have a documented perioperative morbidity and mortality of less than 3%, careful selection of patients, and postoperative management of modifiable risk factors.

Publication Types:
- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 7751850 [PubMed - indexed for MEDLINE]

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1: Cardiovasc Drugs Ther 1994 Apr;8 (2):179-91

Fish oil and the prevention and regression of atherosclerosis.

Sassen LM, Lamers JM, Verdouw PD.

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Epidemiological studies in the seventies have put forward that dietary rather than genetic factors are responsible for the lower incidence of ischemic heart disease in Greenland Inuit and have generated a large body of both in vitro and in vivo experimental studies, exploring the putative favorable effects of fish (oil) on atherogenesis and its risk factors. The first part of this report reviews the in vivo animal studies, concentrating on the hypercholesterolemic models and the arterialized vein graft model. In the hypercholesterolemic animal studies, the results are inconclusive as the studies reporting a protective effect are matched by the number of studies showing no effect or an adverse effect. The diversity in species, dose of fish oil, duration of study, type of vessel studied and type of fish oil preparation (content of n-3 fatty acids, unesterified n-3 fatty acids, ethylesters or triglycerides) could all contribute. Furthermore, the definitions and criteria used in the literature to evaluate atherogenesis are diverse and it appears that while one parameter is affected, another is not necessarily modified in the same direction, stressing the importance of extending the analysis of the effects on atherogenesis to more than one parameter. We also believe that it is time to reach a consensus as to which animal model mimics most closely a particular human situation. Only in appropriate models, investigating more than one atherosclerosis variable, can the effects of a putative anti-atherogenic drug or diet be verified. In the veno-arterial autograft model, mimicking the patient after coronary bypass grafting, dietary fish oil has been consistently effective in preventing accelerated graft intima proliferation. It could therefore be of interest to evaluate the effects of fish oil on graft patency in patients after coronary bypass surgery after a period of years. The results from studies on restenosis after percutaneous transluminal angioplasty are also reviewed and it is concluded that the two large scale trials, that are currently underway, might reliably answer the question whether fish oil is effective as a non-pharmacological adjuvants in the prevention of restenosis. Lastly, the studies on the effects of fish oil on

the regression of experimental atherosclerosis are reviewed. In view of the small number of studies (i.e., four) investigating the effects of fish oil on the regression of atherosclerosis, it is premature to draw any conclusion, and therefore further experimental work is required.

Publication Types:

- Review
- Review, Tutorial

PMID: 7918130 [PubMed - indexed for MEDLINE]
